Pathophysiology of cognitive dysfunction and the role of combined brain/heart magnetic resonance imaging (Review)

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Abstract. Normal cognitive function depends on a continuous and optimally regulated blood supply, and any pathology that further reduces cerebral blood perfusion in addition to that caused by aging could damage or destroy vulnerable neurons of the brain. Furthermore, glucose serves a crucial role as the primary fuel source for the mammalian brain and any disturbance in its circulating concentrations could directly affect brain function. The term cognitive dysfunction (CD), known also as ‘brain fog’, refers to deficits in attention, verbal and non-verbal learning, short-term and working memory, visual and auditory processing, mathematical problem solving, processing speed, focusing on a specific topic, and motor functioning. CD is the end-point of various cardiovascular, neural, metabolic and immune function impairments. Although CD has a serious impact on patient survival and quality of life, usually it is clinically underestimated. CD is currently assessed using cognitive tests (questionnaires), which have important limitations in their diagnostic capacity, specifically in the preclinical forms of CD. Cognitive tests may not identify subclinical cases of CD but diagnose CD only when symptoms are clinically overt. Furthermore, these tests do not provide information regarding the underlying pathophysiologic background of CD. The aim of the present review is to summarize the existing literature on CD and emphasize the role of combined brain/heart magnetic resonance imaging (MRI) in its early diagnosis, before CD questionnaires are abnormal. Combined brain/heart MRI has the potential to identify patients with CD at an early stage, facilitating risk stratification and early intervention. Furthermore, in parallel with brain assessment, it provides valuable information regarding the effect of the underlying disease on the myocardium. Equipment availability, physician familiarity and cost/effectiveness should be considered before wide clinical application of combined brain/heart MRI is recommended.

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Abbreviations: AAV, ANCA-associated vasculitis; ACE, angiotensin-converting enzyme; AD, Alzheimer disease; AF, atrial fibrillation; ALS, amyotrophic lateral sclerosis; aPL, antiphospholipid; ARD, autoimmune rheumatic disease; BMD, Becker muscular dystrophy; BMR, brain magnetic resonance; CD, cognitive dysfunction; CF, cognitive function; CMR, cardiovascular magnetic resonance; CVD, cardiovascular disease; DM, diabetes mellitus; DMD, Duchenne muscular dystrophy; FLAIR, fluid-attenuated inversion recovery; HbA1c, hemoglobin A1c; HF, heart failure; HIV, human immuno-deficiency virus; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; MS, multiple sclerosis; MTX, methotrexate; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; NMDAR, N-methyl-D-aspartate receptor; NPSLE, neuropsychiatric manifestations of SLE; OCD, obsessive-compulsive disorder; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; VaD, vascular dementia; WMH, white matter hyperintensity

Key words: brain, magnetic resonance imaging, cardiovascular, neurological, cognitive dysfunction, cognitive function, heart, dementia, chronic disease
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1. Introduction

Cognition includes intellectual abilities used for perceiving, acquiring, understanding and responding to information presented to a person. The term cognitive dysfunction (CD), known also as ‘brain fog’, refers to deficits in attention, verbal and non-verbal learning, short-term and working memory, visual and auditory processing, mathematical problem solving, processing speed, focusing on a specific topic, and motor functioning (1-3).

It has been documented that normal aging is associated with reduction of cerebral blood flow by approximately 20% at age 60, compared to the age of 20 years (4). Normal cognitive functioning (1-3).

Visual and auditory processing, mathematical problem solving, and non-verbal learning, short-term and working memory, known also as ‘brain fog’, refers to deficits in attention, verbal acquiring, understanding and responding to information presented to a person. The term cognitive dysfunction (CD), known also as ‘brain fog’, refers to deficits in attention, verbal and non-verbal learning, short-term and working memory, visual and auditory processing, mathematical problem solving, processing speed, focusing on a specific topic, and motor functioning (1-3).

Our aim is to review the existing literature about the assessment of CD and the role(s) of various diseases in the development of this disorder. We will emphasize the added value of a combined brain-heart magnetic resonance imaging (MRI) evaluation in the early diagnosis of CD.

2. Indications for CD screening

People should be screened for CD in the following cases: i) if the person himself or herself, family members, or others express concerns about changes in his/her memory or thinking, ii) if problems/changes in the patient's memory or thinking are observed by the physician, iii) if the patient is age 80 or older, because the risk of dementia increases rapidly after this age (7). Other risk factors that could further support the need for dementia screening include: a) low education, b) history of type 2 diabetes mellitus, c) stroke, d) depression, and e) difficulties in managing money or medications (7).

Several standardized measures of CF have been used and include the Montreal Cognitive Assessment (MoCA) (8), the Mini-Mental State Exam (MMSE) (9) and the Mini-Cog (10). All three tests measure mental functions through a series of questions and/or performance of simple tasks. Although cognitive testing cannot show the specific cause of impairment, it can assess whether the patient needs further evaluation (8). The main limitation in the evaluation of CF is the lack of robust evidence to support all available screening tests (11). In addition, they have a relatively high rate of intra-subject variability, which reduces their ability to identify mild deficits or preclinical disease (12). There is no ideal test for any type of CD, and this has resulted in the development of many specialized tests for various types of the disorder (12). Finally, CF testing is unable to provide specific information about the neural structures responsible for any dysfunction identified. For example, although it appears that white matter functions, such as processing speed, attention, and visual-spatial processing, are particularly affected by diabetes mellitus, localization of this dysfunction to white or gray matter is not possible using the standard tests that assess neurocognition (12).

3. Diseases implicated in the development of cognitive dysfunction

Various diseases have been implicated in the development of CD. The main groups responsible for CD development encompass the following entities:

Cardiovascular diseases. Cardiovascular diseases (CVD) are classified as cardiomyopathies, coronary artery, valvular, and congenital heart diseases. All these entities may finally lead to rhythm disturbances and heart failure (HF) (13). Any type of structural or functional CVD decreasing cerebral blood flow will also increase the risk for Alzheimer disease (AD) (14). The association between CVD and CD, known as cardiogenic dementia, was initially described in patients with cardiac arrhythmias (14). Atrioventricular block and arrhythmias lower cardiac output and lead to persistent CD and dementia (14,15). However, CD could be attenuated or even reversed after cardiac pacing (14,15), due to improvement of cerebral perfusion (14).

Brain hypoperfusion, as a result of low cardiac output or hypotension may lead to CD (16) and finally to AD (17-19). There is also an association between atrial fibrillation (AF) and CD leading to AD in the absence of stroke, hypertension and diabetes, because AF induces significant brain hypoperfusion (20,21). Furthermore, HF, thrombotic events, coronary artery disease, valvular disease and AF that are more common in the elderly, can contribute to CD affecting mainly the performance in executive functions, attention, learning, psychomotor speed, verbal fluency, mental alertness and memory (22,23). Additionally, a reduced left ventricular ejection fraction is associated with impairment of continuous vigilance and discriminability (24). Furthermore, low cardiac output is associated with impairment of executive function, including sequencing and planning (25). In these cases, cardiac resynchronization may reverse CD by improving cardiac hemodynamics and consequently brain perfusion (26,27).

Neural diseases. CD is a common expression of various neural disorders including:

Dementias. Several types of dementia have been described: AD, vascular dementia (VaD), dementia with Lewy bodies, frontotemporal dementia and dementia associated with Parkinson's disease. Dementia may also be secondary to the human immuno-deficiency virus (HIV-associated dementia) or other infectious agents and this may be of particular importance in younger adults in specific areas. Other rarer causes of dementia include Huntington's disease, prion disease and head trauma (28).

AD is the most frequent subtype, corresponding to about 55% of all diagnoses in humans aged >65 years (28). Next in frequency is VaD, a common condition, especially in older patients (29,30), estimated to represent 15% of all cases (28). Although AD can be identified with a satisfactory degree of accuracy, at present, there is no consensus on how to define ‘mixed’ dementia in clinical
practice. Moreover, overlapping symptoms and co-morbidities make the distinction more difficult and a differential diagnosis is further complicated by the fact that many patients have concomitant AD and cerebrovascular disease (31).

**Multiple sclerosis.** CD occurs in 40-65% of multiple sclerosis (MS) patients. It involves complex attention, information processing speed, episodic memory and executive functions. It can be found in both subclinical and clinically overt MS. In pediatric-onset MS, cognition worsens relatively rapidly. CD usually affects personal life and vocational status. In relapsing-remitting MS timely and adequate disease-modifying treatment may stabilize or improve CD. Cognitive behavioral therapy, including exercise and education programs, is a promising intervention to improve CD (32).

**Neuromuscular disorders.** Neuromuscular disorders mainly affect the motor functioning of the patient. However, the cognitive effects of these diseases are also important. This is due to molecular defects that significantly affect neuromotor functioning, but also participate in the functioning of neural networks involved in cognitive processes, leading to impairment of executive, behavioral and psychosocial functions (33).

Although most Duchenne muscular dystrophy (DMD) patients are not intellectually disabled, the risk for CD is increased, with up to 30% of DMD patients presenting intellectual disability. Apart from intellectual abilities, neurocognitive dysfunction has been frequently reported. Deficits in short-term memory, executive functions, visuospatial ability, as well as deficits in attention, problems with narrative, linguistic and reading skills have been described, irrespective of general intelligence. Moreover, a higher incidence of neuro-psychiatric disorders, such as autism, attention deficit, hyperactivity, obsessive-compulsive disorders and social behavior problems, has also been reported (34).

**Psychiatric disorders**

**Schizophrenia.** There is a broad range of CD in schizophrenia and includes problems in perception, attention, memory and problem-solving (35). Various studies suggest that the working memory system is of limited capacity in schizophrenia (36-39). Working memory deficits are significantly correlated with formal thought disorders (40), and deficits in long-term memory (41). Schizophrenic patients may also show deficits in executive function (42,43), linked to disease severity and poor medication compliance (44,45).

**Mood disorders.** Neurocognitive deficits are common in mood disorders. In major depression, they can mimic severe dementia (46). In the acute phase of bipolar disorder, they may progress to stupor. Cognitive deficits in mood disorders include impaired performance in tests of attention, executive function and memory. The deficits are correlated with both the number of affective episodes and the overall disease duration (47). Performance on memory and executive tasks has been correlated with illness episodes.

**Obsessive-compulsive disorder.** Patients with obsessive-compulsive disorder (OCD) may show impairment on numerous tests of non-verbal memory including visual reproduction and delayed recognition of figures, maze learning and intermediate/delayed figure copying. Most studies suggest that encoding and retrieval are impaired in OCD, while storage of information remains intact. Patients with OCD often function remarkably well in their daily lives, despite severe symptomatology and cognitive difficulties, which are apparent only on specific testing. In contrast to non-verbal memory deficits, verbal memory is generally preserved in OCD (48,49). Patients with OCD demonstrate normal general intelligence and language abilities.

**Somatic symptoms disorders.** Somatic symptoms disorders include somatic, psychopathological and neuropsychological symptoms. Cognitive complaints include poor concentration, decreased memory of recent events and poor word-finding abilities (50). Approximately 50-85% of patients with somatoform/chronic fatigue syndrome report CD, which contributes significantly to their social and occupational dysfunction (51,52).

**Attention deficit/hyperactivity disorder.** Poor performance on tests of executive function, sustained attention and memory, are the most common neuropsychological deficits reported in children and adults with attention deficit/hyperactivity disorder (ADHD). There is little evidence for deficits in basic motor, visual, spatial or sensory functioning in ADHD, with the possible exception of olfactory function (53,54).

**Substance abuse.** CD has been identified following substance abuse and affects mental activities that involve acquiring, storing, retrieving, and using information. This dysfunction plays an important role in the development of the addictive process and rehabilitation of substance abusers (55-58).

**Metabolic diseases.** The mechanism of CD in diabetes mellitus (DM) is complex and includes a) factors related to DM per se (direct effect of altered glucose metabolism on the brain) and b) DM-related CVD and microvascular dysfunction. Chronic hyperglycemia triggers neuronal damage and endothelial dysfunction, leading to CD over time (59-62). In the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) cognitive follow-up study, 1,144 participants were followed up for 18 years. High long-term hemoglobin A1c (HbA1c) levels, advanced age, lower level of education and two clinical microvascular complications, such as proliferative diabetic retinopathy and nephropathy, were associated with CD (63,64).

DM is also a major risk factor for stroke, particularly ischemic stroke, with type 2 DM alone known to increase stroke risk 1.5 to 4-fold (63). Furthermore, chronic hyperglycemia dramatically increases the risk of diabetic microvascular disease including retinopathy, nephropathy and neuropathy. A positive correlation between nephropathy and/or retinopathy and CD has been found (64,65). Microvascular disease may also directly lead to CD (66).

The effect of DM on cerebrovascular impairment can be explained by the increased burden of inflammatory cytokines e.g., interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), and subsequent chronic inflammation, which contributes to CD (67). Finally, the apolipoprotein E (APOE)
‘4 allele’, a documented risk factor for CVD and AD in the general population, is also implicated in the development of CD in DM. Additionally, studies involving mainly patients with type 2 DM, have revealed APOE ‘4-negative’ diabetic participants to be more likely to develop AD, compared with APOE ‘4-positive’ diabetic patients (68,69).

In contrast to hyperglycemia, the role of hypoglycemia is controversial but the relationship between hypoglycemia and CD may become clear in elderly patients. Although severe hypoglycemia has not been associated with long-term CD in young patients with type 1 DM (DCCT follow-up study) (68), recent studies in adults >60 years with type 1 DM showed a greater prevalence of CD (60).

**Autoimmune rheumatic diseases.** For people with autoimmune rheumatic diseases (ARDs) including sarcoidosis, avoiding CD is crucial to successfully perform everyday tasks, including medical treatment adherence or planning activities. Most ARDs have been associated with various degrees of CD, which has been mainly documented in rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and sarcoidosis.

Combined brain/heart MRI images of a case patient with sarcoidosis and doubtful CD tests, are shown in Figs. 1 and 2.

**Rheumatoid arthritis.** Patients with rheumatoid arthritis (RA) present an increased risk of stroke, as a consequence of accelerated atherosclerosis (70). Among psychiatric manifestations, depression and anxiety have been found in 2/3 of RA patients and have been associated with disease activity (70). RA patients usually underperform on CD tests, compared to controls (71). Even mild CD may influence the functional capacity and quality of life of these patients by affecting reactivity to pain and compliance to treatment (71,72). CD may occur even in the early stages of the disease (73).

Inflammation affecting the brain (72) and accelerated atherosclerosis, as a result of systemic inflammation (74) are the main causes of CD in RA. Furthermore, RA disease activity is an important stimulus of CD, depression and anxiety (72). Finally, pain, stress, fatigue and sleep disturbances, may be also involved in the development of RA-associated CD. Anti-rheumatic drugs, such as methotrexate (MTX) and corticosteroids are also related with CD. Both MTX and corticosteroids suppress systemic inflammation and may have beneficial effects on CD. However, MTX has been associated with CD, mood disturbances and confusion, while corticosteroids may influence memory and hippocampal function (75).

**Systemic lupus erythematosus.** A wide range of syndromes in systemic lupus erythematosus (SLE) including stroke, acute confusional state, headaches and mood disorders may lead to CD (76), which affects 3-81% of SLE patients. This is due to the absence of standardized diagnostic criteria and screening tools. Additionally, the neuropsychiatric manifestations often develop insidiously, can present independently of other SLE signs of disease activity and often do not respond to standard immunosuppression. Therefore, CD in SLE patients often remains underdiagnosed and undertreated in clinical practice (77).

The treatment with neurotoxic/psychoactive medications such as corticosteroids and cyclophosphamide, and the neuropsychiatric manifestations of SLE (NPSLE) such as strokes, seizures, depression or anxiety, can all independently contribute to CD. However, there is an early presentation of NPSLE, with 40% of SLE patients diagnosed with neuropsychiatric symptoms at the time of diagnosis or within the first 3 years post diagnosis (78,79).

Antiphospholipid (aPL) antibodies, often coexisting with SLE, are a strong risk factor for NPSLE, due to a stroke, structural damage and associated CD, as a consequence of hypercoagulation (80,81). However, aPL antibodies have also been correlated to NPSLE syndromes that are not directly related to thrombotic or ischaemic events (82). Neurotoxic auto-antibodies, pro-inflammatory cytokines and cell-mediated agents together
with abnormalities in neuroimmune structures including the choroid plexus and blood-brain barrier, allow systemic autoimmune factors to penetrate into the central nervous system in NPSLE (80,83). Finally, increased levels of IL-6 and neurotoxic anti-N-methyl-D-aspartate receptor (NMDAR) antibodies have been found in SLE with CD (84-86).

**Systemic sclerosis.** Although anxiety, depression and mood changes are common, in contrast to other ARDs, CD is rare in systemic sclerosis. Systemic sclerosis is characterized by a subset of patients who develop CD (87). However, under special circumstances vascular damage can be of great importance, as in a renal crisis. This is due to thrombotic microangiopathy with concurrent hypertension that occurs almost exclusively in early-stage diffuse SSc and is strongly associated with the anti-RNA polymerase autoantibodies. The systemic micro-vasculopathy of SSc renal crisis may lead to generalized seizures and potentially significant CD (88). This disorder generally recovers after several weeks without other consequences. Furthermore, one in five patients with SSc will develop another ARD, such as SLE or Sjögren's syndrome (89) and the CD of these diseases will be an additional factor for CD development in SSc patients. Immune-mediated encephalitis may occasionally occur in some SSc patients (90). SSc is associated with Raynaud's phenomenon and there are several reports of CD after cold exposure (91), due to changes in cerebral perfusion (91). Finally, in localized scleroderma, especially linear morphea, structural abnormalities affecting the cranium or brain can be associated with epilepsy and possibly CD in some patients.

**ANCA-associated vasculitis.** According to a recent study, the prevalence of CD in patients with ANCA-associated vasculitis (AAV) was similar to RA and those with CD had high disease activity. Abnormal performance was more frequent in the executive functions, followed by language. Furthermore, psychomotor functions were more frequently affected in AAV patients (92).

### 4. Currently used approach for CD diagnosis

The currently used diagnostic approach for CD diagnosis includes a) assessment of problems with memory or another mental function; b) mental decline over time; c) if overall mental function and daily activities are affected; and d) mental status testing. A neural clinical and laboratory examination is necessary. Finally, cognitive testing and brain CT/MRI can provide an integrated image of mental status.

The great diversity of causes and outcomes of CD has motivated a wide search for effective therapies. These include specific neurological medications, interventions to achieve better brain perfusion, occupational therapy and environmental approaches.

Future research includes the development of neuroimaging and genetic testing that help the identification of individuals at increased risk for CD.

### 5. Pro and contra of cognitive tests

MoCA is a quick test, taking only 10 to 15 min to be completed. Various studies have shown that MoCA correctly identifies dementia in approximately 94% of cases. Furthermore, while people in the early or mild stages of dementia might score high enough on other tests (including the MMSE), and the score would indicate that no dementia is present, MoCA has been proven effective for showing early-stage dementia, or mild cognitive impairment. Additionally, MoCA is better than the MMSE at indicating if people with Parkinson's disease present signs of Parkinson's disease dementia. However, between the disadvantages of MoCA is the fact that it must be administered and graded by a healthcare professional and therefore an appointment with a nurse, doctor, or therapist is required, in opposition to other tests that can be taken at home. Furthermore, it does not provide a diagnosis, so it must be evaluated together with other tests including brain scans and a neurological testing, before the final diagnosis will be made (93). Finally, in an aging stroke population, hearing loss and visual impairment are problematic for administering a valid MoCA. This limits the generalizability of conclusions that can be drawn from epidemiological studies of CD and its evolution after stroke, although it is recognized that other performance-based cognitive assessment tools suffer from the same limitation (94).

According to published data, cognitive tests are the more clinically useful screening tools for use in community mental health centers. However, because of their poor sensitivity for detecting CD in this patient population, alternative screening methods should be explored. Therefore, there is great clinical need for an objective tool that can assess early the lesion pathophysiology and can predict the future evolution of the patient's CD.

### 6. From cognitive tests to combined brain/heart magnetic resonance imaging

Currently, the role of brain magnetic resonance (BMR) in patients with CD is primarily supportive than diagnostic. American and European guidelines recommend brain imaging to exclude treatable causes, such as tumor, hydrocephalus or intracranial hemorrhage, but also to distinguish between different dementia subtypes. However, this approach depends not only on guidelines, but also on the availability of imaging techniques at individual centers. Advanced MRI techniques, such as functional connectivity MRI, diffusion tensor imaging and magnetic resonance spectroscopy are now becoming available for clinical use in many specialized centers. The increasing research on CD identification at early stages will definitely increase the use of more objective approaches, such as BMR.

BMR is a robust, versatile modality capable to detect early brain alterations without radiation. In patients with long-standing, uncontrolled type 2 DM, white matter hyperintensity (WMH) in BMR has been associated with decreased processing speed (95). WMH is a brain lesion detected as a high-intensity area in MRI T2 and fluid-attenuated inversion recovery images (FLAIR) and reflects damage of small vessels in periventricular and subcortical areas. Although WMH was initially linked to the development of stroke, recently it was clarified that it is also associated with CD. In addition to hypertension, which is the classical risk factor for WMH, there is increasing evidence that DM could also be associated with WMH progression and CD. Although the
Table I. Comparison between testing and combined brain-heart MRI in the detection of CD.

<table>
<thead>
<tr>
<th>CD evaluation method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Location of lesion</th>
<th>Availability</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD testing</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>+++</td>
<td>Low</td>
</tr>
<tr>
<td>Combined brain and heart MRI</td>
<td>++++</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
<td>Very high</td>
</tr>
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CD, cognitive dysfunction; MRI, magnetic resonance imaging. Increasing + symbols indicate increased diagnostic capability of the method.

Factors that accelerate WMH formation in elderly diabetic patients are poorly clarified, it is currently known that insulin resistance is an exacerbating factor. However, hypertension, dyslipidemia and/or other vascular risk factors can also play an important role (96). Furthermore, brain atrophy is present in dementia-free middle-aged adults with type 2 DM. It seems that regional brain atrophy can be developed even in type 2 DM patients with no clinical evidence of microvascular disease. This is probably due to the fact that brain is particularly vulnerable to metabolic alterations prior to peripheral microvascular abnormalities, associated with other target organs (97).

Multiple vascular risk factors, including smoking, hypertension, DM and dyslipidemia are associated with CD. Among them, hypertension is more strongly associated with WMH, possibly due to cerebral microcirculation damage. There is currently evidence that intensive treatment of patients with cardiovascular risk factors, including hypertension and dyslipidemia, can slow down the progression of WMH, compared to untreated controls (98). Furthermore, both atrial fibrillation and HF present high burden of WMH with consequent poorer cognitive performances and depression (92). Finally, complex congenital heart disease, including transposition of the great arteries or univentricular hearts, are associated with neonatal WMH (98).

In Neurology, volumetric MRI is becoming an increasingly important tool in the early detection and monitoring of people suspected to have mild CD and/or AD (93). Furthermore, the BMR evaluation of patients with AD and mild cognitive impairment has revealed early structural changes in the hippocampus, entorhinal cortex, and gray matter structures in the medial temporal lobe. The microstructural integrity of white matter can be studied with diffusion tensor imaging. Increased mean diffusivity and decreased fractional anisotropy are also found in subjects with white matter damage. Recently, magnetization transfer imaging was found to allow the assessment of ongoing global and regional brain damage, independent of atrophy, in patients with AD (99). Finally, WMH distributed in anterior brain regions is related to decline in executive abilities, typical of normal aging, whereas WMH distributed in more posterior brain regions is common in AD. Although epidemiological, observational and pathological studies suggest that WMH may be ischemic in origin and caused by consistent or variable hypoperfusion, there is emerging evidence that it may also reflect vascular deposition of β-amyloid, particularly when it is distributed in posterior areas and is found in patients with AD (100).

In Rheumatology, significant negative correlations between cognitive test scores on verbal memory and number/volume of WMH has been found in SLE, while no significant differences in the number or volume of WMH have been identified between subgroups of SLE patients (101). Furthermore, brain damage due to stroke either ischemic or hemorrhagic and silent vascular damage such as WMH is increased in ARDs (102). The risk of any stroke and BMR findings is worse in inflammatory arthropathies (RA, SLE, AS, gout, psoriatic arthritis) than in noninflammatory arthropathies (OA) (102). Plasma markers of inflammation (C-reactive protein, TNF-α, IL-6) are associated with stroke and increased WMH burden (102).

Although there is an increasing interest about incorporating BMR in the diagnostic algorithm of CD, there is no published evidence about the role of cardiovascular magnetic resonance (CMR) in the evaluation of CD. However, CMR can reveal silent cardiac lesions in both ischemic and nonischemic diseases that may lead to brain hypoperfusion with consequent CD. In this context, CMR was found to detect various phenotypes in diabetic CVD including myocardial scar, ischemia and non-ischemic cardiomyopathy (103). Using the unique capability of CMR to provide sequences dedicated to myocardial function, structure, perfusion, cardiac energetics, lipid metabolism and diffuse extracellular volume expansion, CMR can offer a comprehensive, quantitative and reproducible tool to detect early on silent cardiac lesions in diabetic patients (104,105).

In the Cardiology literature, CMR is represented in the majority of the ESC guidelines (106). It is considered as the modality of choice to perform tissue characterization (differentiation of various types of scars, acute or chronic myocardial inflammation, iron overload), evaluate congenital heart diseases, quantify valvular regurgitation and assess great vessels (106). Furthermore, it is of great clinical significance in the evaluation of arrhythmogenic substrate in patients with ventricular tachycardia and sudden cardiac death (107).

In the Neurology literature, CMR with late gadolinium enhancement (LGE) is the modality of choice for the detection of early cardiac involvement in patients with Duchenne muscular dystrophy (MDM) and Becker muscular dystrophy (BMD) (105). The early detection of cardiac involvement allows the initiation of various drugs including corticosteroids, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and mineralocorticoid receptor antagonists (106).

CMR has been also successfully used to identify vulnerable plaques in the thoracic aorta using 3D multi-contrast CMR and estimate the risk of cerebral embolization using 4D flow CMR.
in cryptogenic stroke patients (101). Although the literature about the use of CMR in the diagnostic algorithm of ischemic stroke is sparse, there are studies demonstrating its potential role in the diagnostic evaluation of cryptogenic stroke to identify potential causes such as cardiac thrombi, cardiac tumors, aortic arch disease and other rare cardiac anomalies (107). CMR can also provide information about functional and structural details of the left atrium and the left atrial appendage that are associated with ischemic stroke risk (108). Finally, cardiac involvement was assessed in amyotrophic lateral sclerosis (ALS) without clinical cardiac symptoms and with a normal cardiac routine assessment. These findings may account for reported cardiac deaths in late-stage ALS patients (109,110).

In the domain of Rheumatology, there is recently a considerable increase in literature regarding the use of CMR for early detection/quantification and disease acuity assessment (oedema/fibrosis imaging) of cardiac involvement in various ARDs. In this context, proposals about the use of CMR in Rheumatology have been already published by a panel of specialists in both Cardiology and Rheumatology (111). Additionally, CMR has been successfully used to clarify the arrhythmogenic substrate in ARDs (111,112).

In contrast to CF testing, a combined MRI of brain/heart can reveal early pathophysiologic changes that are potentially clinically silent but may seriously affect CF. Using this approach, subclinical brain involvement was found to be highly prevalent in ARD patients with cardiac symptoms and was mostly independent of the severity of cardiac involvement (113). It seems that a combined brain/heart MRI can be of value in the detection of CD pathophysiology and potentially facilitate therapeutic risk stratification. However, availability, doctors' familiarity with this approach and high cost should be taken into serious consideration. Finally, studies correlating cognitive tests with brain-heart MRI findings are needed to clarify their interaction in the assessment of CD. Additionally, studies regarding the cost/benefit ratio of this approach are also needed before final conclusions will be drawn. A comparison between CD testing and combined brain-heart MRI in the detection of CD is presented in Table I.

7. Conclusion

CD is the end-point of cardiovascular, neural, metabolic, and immune system impairment. CD testing, which is the most commonly used diagnostic approach, cannot always identify subclinical cases and the underlying pathophysiologic background of CD. A combined brain/heart MRI has the ability to diagnose these patients at an early stage and facilitate the individualization of risk stratification and early intervention. Furthermore, a combined brain-heart MRI is an objective approach that has no limitations of currently used CD tests. However, equipment availability, doctors' familiarity with this approach, and cost effectiveness are at the moment serious obstacles and should be taken into consideration, before brain/heart MRI in the diagnosis of CD is recommended in every day clinical practice.

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Authors' contributions

GMM, FB and SIM recognized the scientific need for a review article on this topic and conceived the study. GMM, FB, GK, MRP, AG, AP, GDK, GPC and SIM designed the study structure, performed the literature search, screened and interpreted the findings. GMM wrote the initial draft, FB and SIM revised the original draft. GK, MRP, AG, AP, GDK and GPC enriched the manuscript and substantially revised the final draft. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent was obtained from the patient for publication of the brain/heart MRI images.

Competing interests

The authors declare that they have no competing interests.

References


